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(54) Benzodiazepine derivatives

Benzodiazepin-Derivate

Derivés de benzodiazépine

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(56) References cited:
EP-A- 0 167 919

- **PROC. NATL. ACAD. SCI. USA, vol. 83, July 1986, pages 4923-4926**

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The file contains technical information submitted after the application was filed and not included in this specification

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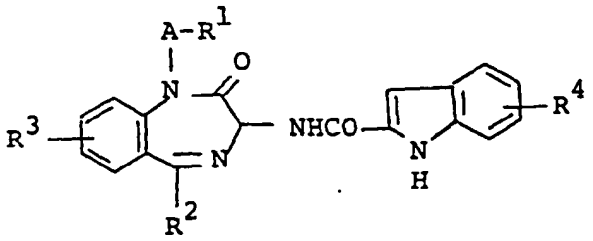
Description

This invention relates to new benzodiazepine derivatives and pharmaceutically acceptable salts thereof.

More particularly, it relates to new benzodiazepine derivatives and pharmaceutically acceptable salts thereof which are cholecystokinin (CCK) antagonists and therefore can be used as therapeutical agents for emesis, pancreatitis, satiety and appetite control, pain control, insulinoma, gastroparesis, acute obstructive cholecystitis, irritable bowel disease, carcinoma of pancreas, etc.

EP-A-0 167 919 discloses benzodiazepine derivatives which are antagonists of cholecystokinin. This document does not mention benzodiazepine derivatives having a heterocyclic group in position R^1. I see formula I, Proc. Natl. Acad. Sci. USA describes a specific benzodiazepine derivative, namely 3S(-)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-1H-indole-2-carbexamide having a CCK-receptor affinity similar to that of CCK itself.

The benzodiazepine derivatives of this invention can be represented by the following formula (I):



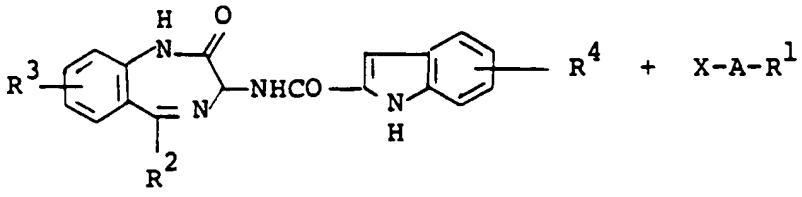
(I)

wherein

R^1 is tetrazolyl or imidazolyl,
R^2 is phenyl which may have a halogen,
R^3 is hydrogen or halogen,
R^4 is hydrogen, halogen or (C_1-C_6) alkoxy and
A is (C_1-C_6) alkylene.

According to the present invention, the new benzodiazepine derivatives (I) can be prepared by the processes which are illustrated in the following scheme.

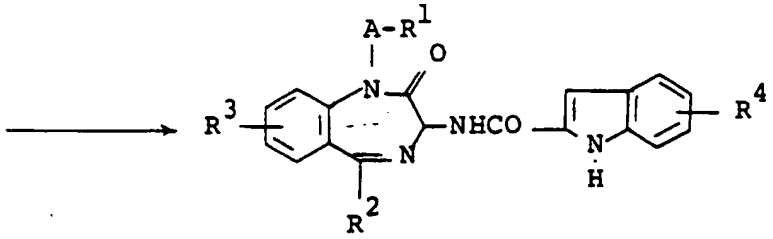
Process 1



(II)
or a salt thereof

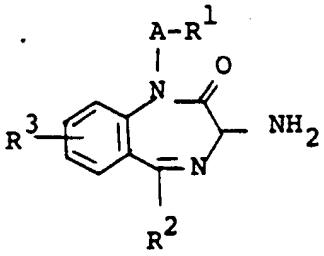
X-A-R^1

(III)
or a salt thereof

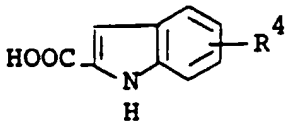


(I)
or a salt thereof

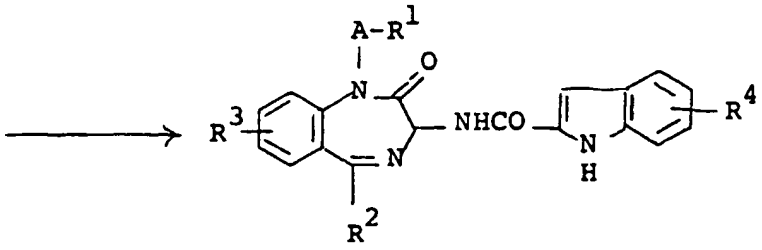
Process 2



(IV)
or its reactive derivative at the amino group
or a salt thereof



(V)
or its reactive derivative at the carboxy group
or a salt thereof



(I)

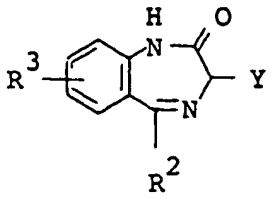
or a salt thereof

wherein

R^1, R^2, R^3, R^4, and A	are each as defined above,
X	is halogen,

The starting compound (IV) is novel and can be prepared by the following processes.

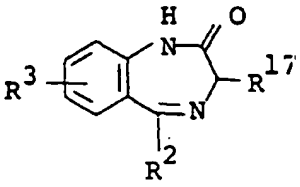
Process A



(VI)

or a salt thereof

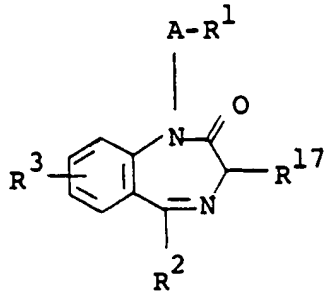
① ↓ $H - R^{17}$ (VII) or a salt thereof



(VIII)

or a salt thereof

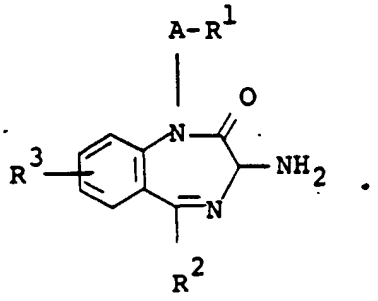
② ↓ $X\text{-}A\text{-}R^{1}$ (III) or a salt thereof



(IX)

or a salt thereof

(3) Elimination reaction of the amino protective group



(IV)

or a salt thereof

wherein

R^1, R^2, R^3, A and X	are each as defined above,
Y	is an acid residue, and
R^{17}	is a protected amino group.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "(C_1-C_6)" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "halogen" C_1-C_6 may include chlorine, bromine, fluorine and iodine.

Suitable "protected amino" may include an acylamino or an amino group substituted by a conventional protective group such as ar (C_1-C_6)alkyl which may have at least one suitable substituent(s), (e.g. benzyl, trityl, etc.) or the like.

Suitable "(C_1-C_6) alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, t-penty-

loxy, hexyloxy and the like, preferably one having 1 to 4 carbon atom(s).

Suitable "(C_1-C_6) alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene or the like, preferably one having 1 to 4 carbon atoms(s).

Suitable "acid residue" may include acyloxy wherein acyl moiety is

(C_1-C_6) alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.);
(C_1-C_6) alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.);
(C_1-C_6) alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.); arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.); aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indancarbonyl, etc.);
ar(C_1-C_6)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.);
ar(C_1-C_6)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

The acyl moiety as stated above may have at least one suitable substituent(s) such as halogen (chlorine, bromine, fluorine and iodine), amino, (C_1-C_6) alkoxycarbonylamino (e.g. methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, tert-butoxycarbonylamino, pentyloxycarbonylamino, hexyloxycarbonylamino, etc.) or the like.

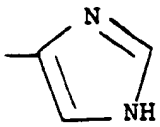
The acid residue may further include halogen (e.g. fluorine, chlorine, bromine and iodine) and the like.

The preferred embodiments of the object compound (I) are as follows.

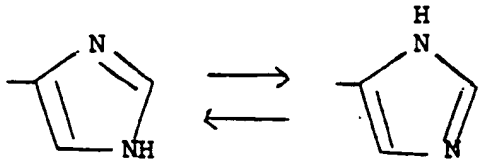
Preferred embodiment of

R^1 is tetrazolyl or imidazolyl
R^2 is phenyl which may have halogen,
R^3 is hydrogen,
R^4 is hydrogen, halogen or (C_1-C_6) alkoxy, and
A is (C_1-C_6) alkylene.

with regard to the object compound (I), in case that the compound (I) has the group of the formula:



said group can also exist in the tautomeric form and such tautomeric equilibrium can be represented by the following scheme.



(A) (B)

Both of the above tautomeric isomers are included within the scope of the present invention. In the present specification and claim, the compounds including the group of such tautomeric isomers are represented for the convenient sake by one expression of the group of the formula (A).

The processes for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1 :

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

Suitable salts of the compounds (II) and (III) can be referred to the ones as exemplified for the compound (I).

This reaction is usually carried out in the presence of base.

Suitable base may include an inorganic base such as alkali metal hydride (e.g. sodium hydride, etc.) alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine or the like.

This reaction is usually carried out in a solvent such as alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 2 :

The compound (I) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the amino group or a salt thereof with the compound (V) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the amino group of the compound (IV) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IV) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IV) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (IV) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (IV) and (V) can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (V) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. The suitable example may be an acid chloride, an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g. methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.), and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (V) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (V) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl 5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(C_1-C_6) alkylamine, pyridine, N-(C_1-C_6)alkylmorpholine, N,N-di (C_1-C_6)-alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

The processes for preparing the starting compound (IV) are explained in the following.

Process A -①:

The compound (VIII) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof. The reaction method and conditions can be referred to those of Preparation 1 as mentioned below.

Process A -②:

The compound (IX) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (III) or a salt thereof. This reaction is carried out by substantially the same method as that of Process 1, and therefore the reaction method and conditions are to be referred to said Process 1.

Process A -③:

The compound (IV) or a salt thereof can be prepared by subjecting the compound (IX) or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compound (IX) can be referred to the ones as exemplified for the compound (I).

The elimination reaction is carried out in accordance with a conventional method such as hydrolysis; reduction; Edman's method (phenyl isothiocyanate method); cr the like. The hydrolysis may include a method using an acid or base or hydrazine and the like. These methods may be selected depending on the kind of the protective groups to be eliminated.

Among these methods, hydrolysis using an acid is one of the most common .and preferable method for eliminating the protective groups such as substituted or unsubstituted alkoxycarbonyl, for example, tert-pentyloxycarbonyl, lower alkanoyl (e.g. formyl, acetyl, etc.), cycloalkoxycarbonyl, substituted or unsubstituted aralkoxycarbonyl, aralkyl (e.g. trityl), substituted phenylthio, substituted aralkylidene, substituted alkylidene, substituted cycloalky-lidene or the like. Suitable acid includes an organic or inorganic acid such as formic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydrochloric acid and the like, and the most suitable acid is an acid which can easily be removed from the reaction mixture by a conventional manner such as distillation under reduced pressure, for example, formic acid, trifluoroacetic acid, hydrochloric acid, etc. The acids can be selected according to the kind of the protective group to be eliminated.

The elimination reaction using trifluoroacetic acid may be carried out in the presence of anisole. The hydrolysis using hydrazine is commonly applied for eliminating a phthaloyl, succinyl type amino-protective group.

The elimination using base is used for eliminating an acyl group such as trifluoroacetyl.
Suitable base may include an inorganic base and an organic base.

The reductive elimination is generally applied for eliminating the protective group, for example, haloalkoxycarbonyl (e.g. trichloroethoxycarbonyl, etc.), substituted or unsubstituted aralkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), 2-pyridylmethoxycarbonyl, etc. Suitable reduction may include, for example, reduction with an alkali metal borohydride (e. g. sodium borohydride, etc.), reduction with a combination of a metal (e.g. tin, zinc, iron, etc.) or the said metal together with a metal salt compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and catalytic reduction. Suitable catalyst includes a conventional one, for example, Raney nickel, platinum oxide, palladium on carbon and the like.

Among the protective groups, the acyl group can generally be eliminated by hydrolysis. Especially, halogen substituted-alkoxycarbonyl and 8-quinolyloxy-carbonyl groups are usually eliminated by treating with a heavy metal such as copper, zinc, or the like.

The reaction is usually carried out in a conventional solvent such as water, chloroform, methylene chloride, alcohol (e.g., methanol, ethanol, etc.), tetrahydrofuran or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and may suitably be selected in accordance with the kind of the amino protective group and the elimination method as mentioned above, and the reaction is usually carried out under a mild condition such as under cooling or at slightly elevated temperature. Among the protective groups, the acyl group derived from α-amino acid can be eliminated by Edman's method.

The object compound (I) and pharmaceutically acceptable salts thereof are CCK antagonists and therefore useful as therapeutical agents for emesis, pancreatitis, etc. In order to show the utility of the object compound (I), CCK an-

tagonism can be shown in the following test method.

CCK receptor antagonism in isolated fundic circular muscle from guinea pig stomach

[I] Test method :

The strip of circular muscle suspended in 25 ml organ bath containing Kreb's bicarbonate solution (NaCl 118mM, KCl 4.8mM, KH_2PO_4 1.2mM, $MgSO_4$ 1.2mM, $CaCl_2$ 2.5mM, $NaHCO_3$ 25mM, glucose 11mM and bovine serum albumin 0.1 %) maintained at 37°C and gassed with 95% O_2 and 5% CO_2.

The strip was placed under an initial tension of 0.5 g and equilibrated for 60 minutes during which the bath volume was replaced every 15 minutes. Isometric contraction was measured using a force transducer. CCK-8 (3.2×10^{-7}M) was added to the bathing solution and the contractile force was measured. After washing out CCK-8, a test compound (1×10^{-5}M) was added. 5 minutes later, CCK-8 was added and the contractile force was measured. CCK antagonism was calculated by comparing the contractile force induced by CCK in the absence or presence of the test compound.

The object compound (I) or pharmaceutically acceptable salts thereof can usually be administered to mammals including human being in the form of a conventional pharmaceutical composition such as capsule, micro-capsule, tablet, granule, powder, troche, syrup, aerosol, inhalation, solution, injection, suspension, emulsion, or the like.

The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g. sucrose, starch, mannit, sorbit, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agent (cellulose, methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g. starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxy-propylstarch, sodium glycole-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g. magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g. citric acid, mentol, glycine, orange powders, etc.), preservative (e.g. sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g. citric acid, sodium citrate, acetic adid, etc.), suspending agent (e.g. methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g. water), base wax (e.g. cacao butter, polyethyleneglycol, white petrolatum, etc.).

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight, conditions of the patient or the administering method.

The following preparations, references and examples are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

A mixture of (3RS)-1,3-dihydro-3-acetoxy-5-phenyl-2H-1,4-benzodiazepine-2-one (11.75 g), potassium phthalimide (11.1 g), sodium iodide (60 g) and N,N-dimethylformamide (80 ml) was stirred for 45 minutes at 90 to 95°C. The reaction mixture was poured into a cold water (1 ℓ). The precipitates were collected by filtration, washed with water and recrystallized from ethanol to give (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-2H-1,4-benzodiazepine-2-one (8.32 g).

IR (Nujol) : 3500, 3370, 3230, 1780, 1720, 1695, 1610, 1575 cm^{-1}
NMR (DMSO-d_6, δ) : 5.73 (1H, s) , 7.30-7.70 (9H, m) , 7.97 (4H, m), 11.90 (1H, br s)

Preparation 2

A mixture of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-2H-1,4-benzodiazepine-2-one (8.2 g), hydrazine hydrate (1.08 g) and tetrahydrofuran (160 ml) was stirred for 1.0 hour at room temperature and heated under reflux for 1.5 hours. After the precipitates were filtered off, the filtrate was evaporated to small volume and the equivalent volume of diisopropyl ether was added thereto. The precipitates were collected by filtration to give (3RS)-1,3-dihydro-3-amino-5-phenyl-2H-1,4-benzodiazepine-2-one (3.64 g).

IR (Nujol) : 3360, 3290, 2700, 1670, 1600, 1570, 1480 cm^{-1}
NMR (DMSO-d_6, δ) : 4.30 (1H, s), 5.0 (2H, br s), 7.20-7.60 (9H, m)

Preparation 3

To a solution of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-2H-1,4-benzodiazepine-2-one (1.90 g) in N,N-dimeth-

ylformamide (30 ml) was added sodium hydride (62% suspension in mineral oil; 0.20 g) gradually with stirring under cooling in an ice-bath (<3°C). The mixture was stirred for 10 minutes under the same conditions. To the resultant mixture was added 2-[(tetrahydropyran-2-yl)oxy]ethyl bromide (1.60 g) in one portion. The mixture was stirred at ambient temperature for one hour and at 45°C for 4.5 hours and allowed to stand overnight. The resultant reaction mixture was poured into water and extracted with ethyl acetate twice. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave light yellow powder, which was washed with a mixture of ethyl acetate and diethyl ether and collected by filtration to afford a mixture (1.48 g) of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-1-{2-((RS)-2-tetrahydropyranyloxy) ethyl}- 2H-1,4-benzodiazepine-2-one and (3RS)-1,3-dihydro-5-phenyl-3-phthalamido-1-{-2-((SR)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one.

IR (Nujol): 1770, 1714, 1670, 1600, 1375, 1130, 1014, 710 cm^{-1}
NMR ($CDCl_3$, δ): 1.3-1.9 (6H, broad), 3.4-4.7 (7H, m), 6.00 (1H, s), 7.3-8.1 (13H, m)

Preparation 4

To a solution of a mixture (0.51 g) of (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-1-{2-((RS)-2-tetrahydropyranyloxy) ethyl}-2H-1,4-benzodiazepine-2-one and (3RS)-1,3-dihydro-5-phenyl-3-phthalimido-1-{2-((SR)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one in chloroform (10 ml) was added hydrazine hydrate (55 mg) at ambient temperature under stirring. The mixture was stirred for 1.5 hours under the same conditions and heated under reflux for 1.5 hours. After cooling, the resultant precipitate was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in a small amount of ethanol and diethyl ether was added thereto. White powder was filtered off again and the filtrate was evaporated to give a crude mixture (0.43 g) of (3RS)-1,3-dihydro-5-phenyl-3-amino-1-{2-((RS)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one and (3RS)-1,3-dihydro-5-phenyl-3-amino-1-{2-((SR)-2-tetrahydropyranyloxy)ethyl}-2H-1,4-benzodiazepine-2-one.

IR (Nujol): 3340, 1680, 1660, 1600, 780, 760, 695 cm^{-1}

Example 1

To a solution of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (1.18 g) in N,N-dimethylformamide (30 ml) was added sodium hydride (62% suspension in mineral oil; 0.26 g) under stirring and cooling at 0°C in an ice-salt bath in a nitrogen stream atmosphere. After the mixture was stirred for 40 minutes under the same conditions, 5-chloromethyltetrazole (0.39 g) was added thereto. The resultant mixture was stirred at ambient temperature for 66 hours. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and the aqueous solution was washed with ethyl acetate. After removal of a small amount of insoluble material by filtration, the separated aqueous layer was acidified with diluted hydrochloric acid.

The acidified aqueous mixture was extracted with ethyl acetate twice and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent afforded an orange oil (1.27 g), which was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (10:1) to give the desired pure product of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-1-(5-tetrazolylmethyl)-2H-1,4-benzodiazepine-2-one (0.5 g).

mp: 190-195°C (dec.)
IR (Nujol): 3350 (sh), 3250, 1680, 1635, 1600, 740, 695 cm^{-1}
NMR (DMSO-d_6, δ): 5.42 (2H, ABq), 5.70 (1H, d, J=8.0Hz), 6.9-8.0 (15H, m), 9.44 (1H, d, J=8.0Hz), 11.6 (1H, broad s)
Mass: m/e = 447 (M^+)

Preparation 5

(1) To a solution of a mixture (1.0 g) of (3R)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one in N,N-dimethylformamide (5 ml) was added sodium hydride (77.4 mg, 62% suspension in mineral oil) under stirring with cooling in an ice-bath (ca. 3°C). The mixture was stirred for 40 minutes under the same condition. To the resultant mixture was added 2-acetoxyethyl bromide (0.37 g) at once under stirring and cooling. The mixture was stirred for 1.5 hours under ice-cooling and for 2 hours at ambient temperature. The reaction mixture was poured into water and extracted with ethyl acetate twice. The extracts were combined, washed with brine and dried over magnesium sulfate. Removal of the solvent by evaporation gave an oil (1.29 g), which was subjected to column chromatography on silica gel with an eluent of a mixture of chloroform and ethyl acetate

(10:1). The fractions containing the desired compound were combined and evaporated to afford a colorless oily mixture (0.84 g) of (3R)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one.

IR (liquid) : 3400 (shoulder), 3300, 1730, 1700 (shoulder), 1690, 1660, 1600, 745, 695 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (9H,s), 1.62 (3H, s), 3.0-3.3 (2H, m), 3.9-4.2 (3H, m), 4.4-4.8 (2H, m), 5.06 (1H, broad d), 5.51 & 5.53 (1H, d & d), 7.2-7.85 (14H, m)

The following compound was obtained according to a similar manner to that of Preparation 5(1).

(2) Mixture of (3R)-1-(2-acetoxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-3-[(2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one

IR (liquid) : 3400 (shoulder), 3320, 1730, 1700 (shoulder), 1690, 1662, 1485, 1440, 1380, 1365, 1230, 1161, 1048, 750, 695 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (9H, s), 1.79 (3H, s), 3.0-3.3 (2H, m) , 3.8-4.8 (5H, m) , 5.07 (1H, broad d, J=7.4Hz), 5.53, 5.55 (1H, dd, J=8Hz), 6.95-7.9 (14H, m)

Preparation 6

To a solution of a mixture (0.7 g) of (3R)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-1,3-dihydro-5-phenyl-3-[((2S)-2-tert-butoxycarbonylamino-3-phenylpropanoyl)amino]-2H-1,4-benzodiazepine-2-one in ethyl acetate (20 ml) was introduced hydrogen chloride gas under cooling in an ice-bath with stirring. After the solution was saturated with hydrogen chloride, the mixture was stirred for 30 minutes under the same temperature and for 1 hour at ambient temperature. After removal of the hydrogen chloride by bubbling dried nitrogen gas, the mixture was evaporated under reduced pressure. To the residue was added water and the mixture was neutralized with a saturated aqueous solution of sodium bicarbonate. The mixture was extracted with ethyl acetate twice and the extract was washed with water and dried over magnesium sulfate. Removal of the solvent afforded a mixture (0.57 g) of (3R)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one and (3S)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one.

Preparation 7

A mixture (12.2 g) of (3R)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (3R-isomer) and (3S)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (3S-isomer) was subjected to a column chromatography on silica gel (230-400 mesh) with an eluent of a mixture of chloroform and methanol (20:1). The fractions containing the object compound were combined and evaporated to dryness to give pure 3S-isomer (3.32 g) as an oil. From the other fractions, an oily mixture (8.50 g) of 3S-isomer and 3R-isomer was obtained. The oily mixture was re-chromatographed on silica gel (230-400 mesh) with an eluent of a mixture of chloroform and methanol (15:1) to give an oily pure 3S-isomer (1.30 g) and an oily pure 3R-isomer (4.01 g).

NMR ($CDCl_3$ + D_2O, δ) 270 MHz :

3S-isomer
1.648 (3H, s), 2.817 (1H, dd, J=14.0Hz, 10.8Hz), 3.336 (1H, dd, J=14Hz, 6.5Hz), 3.704 (1H, dd, J=10.8Hz, 6.5Hz), 3.927 (1H, dt, J=15.1Hz, 6.5Hz), 4.07-4.20 (2H, m), 4.660 (1H, octet, J=13.6Hz, 7.6Hz, 7.6Hz), 5.578 (1H, s), 7.19-7.64 (14H, m)

3R-isomer
1.642 (3H, s), 2.696 (1H, dd, J=14.0Hz, 10.8Hz), 3.349 (1H, dd, J=14.0Hz, 6.5Hz), 3.729 (1H, dd, J=10.8Hz, 6.5Hz), 3.927 (1H, dt, J=15.1Hz, 6.5Hz), 4.09-4.17 (2H, m), 4.690 (1H, octet, J=13.6Hz, 7.6Hz, 7.6Hz), 5,571 (1H, s), 7.21-7.63 (14H, m)

Preparation 8

The following compounds were obtained according to similar manners to those of Preparations 6 and 7.

(3S)-1-(2-Acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

mp :	168-170°C
IR (Nujol) :	3410, 3360, 3325 (sh), 1742, 1680 (sh), 1667, 1610 (sh), 1600, 1480, 1448, 1240, 1108, 1045, 810, 781, 730, 699 cm^{-1}
NMR ($CDCl_3$, δ) :	1.81 (3H, s), 1.85 (2H, s), 2.84 (1H, dd, J=10.5Hz, 13.5Hz), 3.33 (1H, dd, J=13.5Hz, 4Hz), 3.69-4.25 (4H, m), 4.5-4.8 (1H, m), 5.60 (1H, d, J=8Hz), 6.95-7.9 (13H, m), 9.01 (1H, d, J=9Hz)

(3R)-1-(2-Acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

IR (Film) :	3400 (sh) , 3360, 1738, 1685 (sh), 1668, 1605, 1510 (sh), 1495, 1450, 1380, 1328, 1240, 1220, 1108, 1045, 820, 750, 700 cm^{-1}
NMR ($CDCl_3$, δ) :	1.80 (3H, s), 1.87 (2H, s), 2.73 (1H, dd, J=13.5Hz., 10.5Hz), 3.39 (1H, dd, J=13.5Hz, 4Hz), 3.7-4.25 (4H, m), 4.5-4.8 (1H, m), 5.61 (1H, d, J=8Hz), 6.95-7.9 (13H, m), 9.04 (1H, d, J=8Hz)

Preparation 9

(1) A solution of (3S)-1-(2-acetoxyethyl)-3-[((2S)-2-amino-3-phenylpropanoyl)amino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (4.65 g) and phenyl isothiocyanate (1.43 g) in methylene chloride (100 ml) was heated on steam bath under stirring. After removal of the solvent, methylene chloride (100 ml) was added to the residue. The procedure described above was repeated three times. Then the methylene chloride was removed completely under reduced pressure to give an oily intermediate (thiourea derivative). To the oil was added trifluoroacetic acid (80 ml) and the mixture was warmed on water bath set at 52°C under stirring for 20 minutes. Removal of the solvent under reduced pressure and the residue was treated with methylene chloride and diethyl ether twice respectively to give an viscous red oil, which was subjected to column chromatography on silica gel with an eluent of a mixture of chloroform and methanol (15:1). The fractions containing the desired compound were combined and evaporated to afford an orange oil (2.24 g). The oil was dissolved in ethyl acetate and washed with a small amount of an aqueous solution of sodium bicarbonate. The organic layer was separated and dried over magnesium sulfate. Removal of the solvent gave (3S)-1-(2-acetoxyethyl)-3-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (1.35 g) .

IR (Film) :	3370, 3300, 1725, 1665, 1600 cm^{-1}
NMR ($CDCl_3$, δ) :	1.66 (3H, s), 2.90 (2H, br s), 3.8-4.8 (5H, m), 7.1-7.8 (9H, m)
$[\alpha]_D^{26.8}$:	-111.73° (0.00260 g/ml, $CHCl_3$)

The following compounds were obtained according to a similar manner to that of Preparation 9(1).

(2) (3R) -1-(2-Acetoxyethyl)-3-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one

IR (Film) :	3370, 3300, 1725, 1665, 1600 cm^{-1}
NMR ($CDCl_3$, δ) :	1.66 (3H, s), 2.89 (2H, br s), 3.8-4.8 (5H, m), 7.1-7.8 (9H, m)
$[\alpha]_D^{26.8}$:	123.63° (0.00312 g/ml, $CHCl_3$)

(3) (3S)-1-(2-Acetoxyethyl)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

IR (Film) :	3450 (sh), 3380, 3325 (sh), 1738, 1680, 1660 (sh), 1605, 1580, 1490, 1455, 1375, 1332, 1230, 1110, 1050, 820, 760, 745 cm^{-1}
NMR ($CDCl_3$, δ) :	1.81 (3H, s), 3.8-4.8 (6H, m), 6.95-7.9 (9H, m)
$[\alpha]_D^{25}$:	-57.68° (3.10 mg/ml, CH_2Cl_2)

(4) (3R)-1-(2-Acetoxyethyl)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

IR (Film) :	3450 (sh), 3350, 3325 (sh), 1736, 1690 (sh), 1673, 1650 (sh), 1600, 1580, 1482, 1450, 1370, 1328, 1222, 1105, 1000, 815, 750 cm^{-1}
NMR ($CDCl_3$, δ) :	1.80 (3H, s), 3.8-4.8 (6H, m), 6.95-7.9 (9H, m)
$[\alpha]_D^{25}$:	50.52° (3.18 mg/ml, CH_2Cl_2)

Reference 1

To a solution of (3S)-1-(2-acetoxyethyl)-3-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (1.35 g) in N,N-dimethylformamide (25 ml) were added indole-2-carboxylic acid (0.64 g), N-hydroxybenzotriazole (0.54 g) and N, N'-dicyclohexylcarbodiimide (0.83 g) under stirring at ambient temperature. The mixture was stirred for 2 hours at the same temperature and allowed to stand overnight. The resultant precipitates were filtered off and the filtrate and the washings were combined. The solvent (N,N-dimethylformamide) was evaporated under reduced pressure. To the residue was added water and the mixture was extracted with ethyl acetate. The extract was washed with brine twice and dried over magnesium sulfate. Removal of the solvent afforded an oil (3.05 g), which was subjected to column chromatography on silica gel with an eluent of a mixture of chloroform and methanol (15:1). The fractions containing the desired product were combined and evaporated under reduced pressure to give (3S)-1-(2-acetoxyethyl)-3-(2-indolylcarbonylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (1.90 g).

IR (Nujol) :	3325, 3260, 1735, 1680, 1630, 1600, 1230, 745, 697 cm^{-1}
NMR($CDCl_3$, δ) :	1.65 (3H, s), 3.8-4.3 (3H, m), 4.55-4.9 (1H, m) , 5.84 (1H, d, J=8.25Hz), 7.0-7.8 (14H, m), 8.14 (1H, d, J=8.25Hz), 9.98 (1H, br s)
MASS :	m/e=481(M^+)
$[\alpha]_D^{26.8}$:	-51.27° (0.00340 g/ml, $CHCl_3$)

Reference 2

To a solution of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (394 mg) in N,N-dimethylformamide (4 ml) was added sodium hydride (62% suspension in mineral oil, 44 mg) under stirring at 0°C in an ice-bath. The mixture was stirred for 1.0 hour at 0 to -5°C. 2-Methoxyethyl chloride (142 mg) was added thereto. The mixture was stirred for 6.0 hours at 60 to 70°C and cooled. To the cooled reaction mixture were added acetic acid (0.5 ml), ethyl acetate (40 ml) and water (40 ml) under stirring. The organic layer was separated, washed with an aqueous solution of sodium bicarbonate and water, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel with chloroform as an eluent to give the pure product of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-1-(2-methoxyethyl)-2H-1,4-benzodiazepine-2-one (110 mg).

mp :	180-185°C (dec.)
IR (Nujol) :	3440, 3275, 1685, 1630, 1600, 1540, 1490 cm^{-1}
NMR ($CDCl_3$, δ) :	3.13 (3H, s), 3.45-3.65 (2H, m), 3.80-4.50 (2H, m) , 5.80 (1H, d, J=8Hz), 7.0-7.80 (14H, m), 8.15 (1H, d, J=8Hz), 9.75 (1H, s)

Example 2

(1) To a mixture of (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-2H-1,4-benzodiazepine-2-one (800 mg), 1-trityl-4-chloromethylimidazole hydrochloride (790 mg) and N,N-dimethylformamide (16 ml) was added sodium hydride (62 % suspension in mineral oil, 168 mg) under stirring and cooling at 0 °C in an ice-bath. The mixture was stirred for 30 minutes at 0 to 5 °C and heated at 70 to 80 °C for 3.0 hours. To the cooled reaction mixture were added acetic acid (2.0 ml) and 6N hydrochloric acid (5 ml). The mixture was stirred for 1.0 hour at 60 °C. The cooled reaction mixture was poured into a mixture of ethyl acetate (100 ml) and water (100 ml) under stirring. The organic layer was separated, washed with water three times, dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (20:1) to give (3RS)-1,3-dihydro-3-(2-indolylcarbonylamino)-1-(4-imidazolylmethyl)-5-phenyl-2H--1,4-benzodiazepine-2-one (306.0 mg).

mp:	195-200 °C (dec.)
IR (Nujol):	3250, 1680, 1635, 1600, 1530 cm^{-1}
NMR ($CDCl_3$, δ):	4.93: (2H, s), 5.75 (1H, d, J=8Hz), 6.78 (1H, s) , 7.0-7.85 (15H, m) , 8.35 (1H, d, J=8Hz), 10.35 (1H, broad s)
MASS:	m/e=474 (M^+)

The following compounds were obtained according to a similar manner to that of Example 2 (1).

(2) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(4-imidazolylmethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

mp : 205-210°C (dec.)
NMR ($CDCl_3$, δ) : 4.85, 5.10 (2H, ABq, J=15Hz), 5.80 (1H, d, J=8Hz), 6.80-7.83 (15H, m), 8.10 (1H, d, J=8Hz), 10.10 (1H, broad s)
MASS : m/e=492 (M^+)

(3) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(2-imidazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 175-180°C (dec.)
NMR (DMSO-d_6, δ) : 5.10 (2H, s), 5.65 (1H, d, J=8Hz), 6.60-8.10 (16H, m), 9.36 (1H, d, J=8Hz), 11.65 (1H, br s), 11.90 (1H, br s)
MASS : m/e=474 (M^+)

(4) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-[2-(4-imidazolyl)ethyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

mp : 185-190°C (dec.)
NMR (DMSO-d_6, δ) : 2.63 (2H, t, J=7Hz), 3.85-4.20 (1H, m), 4.20-4.75 (1H, m), 5.55 (1H, d, J=8Hz), 6.60 (1H, s), 6.93-7.85 (15H, m), 9.43 (1H, d, J=8Hz), 11.65 (1H, br s)
MASS : m/e=488 (M^+)

Preparation 10

To a suspension of (3RS)-1,3-dihydro-5-(2-fluorophenyl)-3-phthalimido-2H-1,4-benzodiazepine-2-one (1.0 g) and 1-trityl-4-chloromethylimidazole hydrochloride (1.28 g) in N,N-dimethylformamide (25 ml) was added sodium hydride (40% suspension in mineral oil, 0.36 g) gradually under stirring and cooling in an ice-bath, and the mixture was stirred at the same temperature for one hour and then at ambient temperature for 17 hours. After addition of acetic acid (0.5 ml), the reaction mixture was poured into water (100 ml). The mixture was adjusted to pH 7 with an aqueous sodium bicarbonate under stirring. The resultant precipitates were collected by filtration, washed with water and dried under reduced pressure and warming to give yellow powder (2.22 g). The powder was purified by column chromatography on silica gel with an eluent of a mixture of chloroform and ethyl acetate (20:1) to afford (3RS)-1,3-dihydro-5-(2-fluorophenyl)-3-phthalimido-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (1.38 g).

NMR (DMSO-d_6, δ) : 5.08 (2H, ABq), 5.75 (1H, s), 6.7-7.7 (29H, m)

Preparation 11

To a suspension of (3RS)-1,3-dihydro-5-(2-fluorophenyl)-3-phthalimido-1-(1-trityl-4-imidazolyl)-methyl-2H-1,4-benzodiazepine-2-one (19.96 g) in tetrahydrofuran (200 ml) was added a solution of hydrazine hydrate (1.38 g) in methanol (10 ml). The mixture was stirred at ambient temperature for 0.5 hour and then the resultant clear solution was refluxed for 2 hours under stirring. The reaction mixture was cooled in an ice-bath and the precipitates were filtered off. The filtrate and washings were evaporated under reduced pressure. The residue was dissolved in chloroform and the mixture was filtered. The filtrate was evaporated to give an oil (19.30 g), which was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (30:1) to afford (3RS)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (9.97 g).

NMR ($CDCl_3$, δ) : 2.42 (2H, broad s), 4.49 (1H, s), 5.06 (2H, s), 6.8-8.0 (25H, m)

Preparation 12

(1) To a solution of (3RS)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (591.7 mg) in ethyl acetate (2 ml) was added a solution of (S)-(+)-mandelic acid (129.3 mg) in ethyl acetate (4 ml) under stirring at ambient temperature. The precipitated gel was dissolved by addition of methanol (0.2 ml). To the clear solution were added ethyl acetate (4 ml) and diisopropyl ether (three drops). The mixture was stirred for 2 hours and allowed to stand overnight. The resultant precipitates were collected by filtration, washed with ethyl acetate and diisopropyl ether and dried to give white powder (202.2 mg), which was recrystallized from ethyl acetate to afford (S)-(+)-mandelic acid salt of (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one as crystals.

$[\alpha]_D^{24}$ = -33.33° (C=0.846, CH_3OH)

Further, a mixture of (3R)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one and (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one was obtained from the filtrate.

(2) (S)-(+)-Mandelic acid salt of (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trytyl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one obtained in Preparation 12(1) was suspended in a mixture of water and ethyl acetate. The resultant mixture was adjusted to pH 7-8 with an aqueous solution of sodium bicarbonate under stirring. The organic layer was separated, washed with water and evaporated to dryness to give (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (181.4 mg).

$[\alpha]_D^{24}$ = -35.34° (C=0.846, CH_3OH)

Preparation 13

(1) A mixture ($[\alpha]_D$ = +14.4°) (1.57 g) of (3R)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one and (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one obtained in Preparation 12(1) was dissolved in a mixture of ethyl acetate (5.3 ml) and methanol (0.5 ml). To a solution was added a solution of (R)-(-)-mandelic acid (342.7 mg) in ethyl acetate (20 ml) under stirring at ambient temperature. To the mixture was added diisopropyl ether (0.5 ml) and the resultant mixture was stirred for 2 hours and allowed to stand overnight. The precipitates were collected by filtration, washed with ethyl acetate and diisopropyl ether and dried to give (R)-(-)-mandelic acid salt of (3R)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (white powder, 685.6 mg).

$[\alpha]_D^{24}$ = +33.60° (C=0.848, CH_3OH)

(2) (3R)-1,3-Dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one was obtained by treating (R)-(-)-mandelic acid salt of (3R)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one in a similar manner to that of Preparation 12(2).

$[\alpha]_D^{22}$ = +37.91° (C=0.844, CH_3OH)

Example 3

The following compounds were obtained according to a similar manner to that of Reference 2.

(1) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(4-imidazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

IR (Nujol): 3250, 1680, 1635, 1600, 1530 cm^{-1}

(2) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(4-imidazolylmethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR ($CDCl_3$, δ): 4.85, 5.10 (2H, ABq, J=15Hz), 5.80 (1H, d, J=8Hz), 6.80-7.83 (15H, m), 8.10 (1H, d, J=8Hz), 10.10 (1H, broad s)

(3) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ): 5.04 (2H, ABq), 5.63 (1H, d, J=7.9Hz), 6.9-8.2 (15H, m), 9.58 (1H, d, J=7.9Hz), 11.65 (1H, s), 11.92 (1H, s)

(4) (3R)-1,3-Dihydro-l-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ): 5.04 (2H, ABq), 5.62 (1H, d, J=7.9Hz), 6.9-8.3 (15H, m), 9.58 (1H, d, J=7.9Hz), 11.66 (1H, s), 11.93 (1H, s)

(5) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(2-imidazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ): 5.10 (2H, s), 5.65 (1H, d, J=8Hz), 6.60-8.10 (16H, m), 9.36 (1H, d, J=8Hz), 11.65 (1H, br s), 11.90 (1H, br s)

(6) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-[2-(4-imidazolyl)ethyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ): 2.63 (2H, t, J=7Hz), 3.85-4.20 (1H, m), 4.20-4.75 (1H, m), 5.55 (1H, d, J=8Hz), 6.60 (1H, s), 6.93-7.85 (15H, m), 9.43 (1H, d, J=8Hz), 11.65 (1H, br s)

(7) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one hydrochloride

NMR (DMSO-d_6, δ): 5.33 (2H, ABq), 5.69 (1H, d, J=7.6Hz), 7.0-8.0 (15H, m), 9.05 (1H, s), 9.60 (1H, d, J=7.6Hz), 11.74 (1H, s), 14.73 (1H, broad s)

Preparation 14

A mixture of (3S)-1,3-dihydro-5-(2-fluorophenyl)-3-amino-1-(1-trityl-4-imidazolyl)methyl-2H-1,4-benzodiazepine-2-one (0.79 g), indole-2-carboxylic acid (0.22 g), N-hydroxybenzotriazole (0.18 g) and N,N'-dicyclohexylcarbodiimide (0.28 g) in N,N-dimethylformamide (8 ml) was stirred at ambient temperature overnight and filtered. The filtrate and washings were diluted with ethyl acetate. The mixture was washed with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a viscous oil (1.12 g), which was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (30:1) to afford (3S)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (amorphous substance, 0.97 g).

$[\alpha]_D^{23}$ = -32.47° (C=0.85, CH_3OH)

NMR ($CDCl_3$, δ): 5.085 (2H, ABq), 5.76 (1H, d, J=7.9Hz), 6.8-8.0 (30H, m), 8.10 (1H, d, J=7.9Hz), 9.81 (1H, s)

Preparation 15

To a solution of (3R)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (0.81 g), indole-2-carboxylic acid (0.23 g), N-hydroxybenzotriazole (0.19 g) in N,N-dimethylformamide (8 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.27 g) and triethylamine (0.14 g) under stirring at ambient temperature. The mixture was stirred for 4 hours at ambient temperature. To the reaction mixture were added ethyl acetate and water under stirring. The mixture was adjusted to pH 8 with an aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The separated organic layer and the extract were combined, washed with water twice and dried over magnesium sulfate. The solvent was removed under reduced pressure to give (3R)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (1.0 g).

$[\alpha]_D^{22}$ = +41.58° (C=0.856, CH_3OH)

NMR (DMSO-d_6, δ): 5.11 (2H, ABq), 5.64 (1H, d, J=8.0Hz), 6.7-8.0 (30H, m), 9.55 (1H, d, J=8.0Hz), 11.66 (1H, s)

Example 4

To a solution of (3S)-1,3-dihydro-1-(1-trityl-4-imidazolyl)methyl-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (1.0 g) in N,N-dimethylformamide (10 ml) was added 6N hydrochloric acid (7 ml) under stirring and cooling in an ice-bath. The mixture was warmed to 50°C and stirred for 2 hours.

After cooling to room temperature, to the reaction mixture were added water and ethyl acetate under stirring. The mixture was adjusted to pH 8 with an aqueous solution of sodium bicarbonate. The separated organic layer was washed with water and dried. Removal of the solvent gave a viscous oil (1.20 g), which was chromatographed on silica gel with an eluent of a mixture of chloroform and methanol (20:1) to afford (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (601.5 mg) as an yellow crystalline powder.

$[\alpha]_D^{20}$ = +24.68° (C=0.64, $CHCl_3$)

NMR (DMSO-d_6, δ): 5.04 (2H, ABq), 5.63 (1H, d, J=7.9Hz), 6.9-8.2 (15H, m), 9.58 (1H, d, J=7.9Hz), 11.65 (1H, s), 11.92 (1H, s)

Example 5

The following compound was obtained according to a similar manner to that of Example 4.

(3R)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

$[\alpha]_D^{25}$ = -26.40° (C=0.64, $CHCl_3$)

NMR (DMSO-d_6, δ): 5.04 (2H, ABq), 5.62 (1H, d, J=7.9Hz), 6.9-8.3 (15H, m), 9.58 (1H, d, J=7.9Hz), 11.66 (1H, s), 11.93 (1H, s)

Example 6

To a solution of (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (215.1 mg) in methanol (5 ml) was added 6N-hydrogen chloride solution in ether (0.1 ml) under cooling. The clear yellow solution was evaporated to dryness under reduced pressure. The residue was triturated in ether to afford yellow powder, which was collected by filtration and washed twice with ether to give (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one hydrochloride (197.1 mg).

$[\alpha]_D^{24}$ = 35.94° (C=0.612, CH_3OH)

mp: 214-218°C (dec.)

NMR (DMSO-d_6, δ): 5.33 (2H, ABq), 5.69 (1H, d, J=7.6Hz), 7.0-8.0 (15H, m), 9.05 (1H, s), 9.60 (1H, d, J=7.6Hz), 11.74 (1H, s), 14.73 (1H, broad s)

Example 7

To a solution of (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one (246 mg) in methanol (10 ml) was added L-(+)-tartaric acid (75.0 mg) at room temperature. After being stirred for several minutes, the mixture was concentrated to 2 ml. The resultant light yellow powder was collected by filtration, washed with diisopropyl ether twice and dried to give (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one L-(+)-tartrate (235.3 mg).

mp: 170-175°C (dec.)

NMR (DMSO-d_6, δ): 4.31 (2H, s), 5.07 (2H, s), 5.63 (1H, d, J=7.7Hz), 6.9-8.1 (15H, m), 9.58 (1H, d, J=7.7Hz), 11.65 (1H, s)

Example 8

The following compound was obtained by reacting (3S)-1,3-dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one with methanesulfonic acid in similar manners to those of Examples 6 and 7.

(3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one methanesulfonate

$[\alpha]_D^{24}$ = -31.32° (C=0.632, CH_3OH)

mp: 136-139°C (dec.)

NMR (DMSO-d_6, δ): 2.39 (3H), 5.33 (2H, ABq), 5.69 (1H, d, J=7.7Hz), 7.0-7.8 (15H, m), 8.99 (1H, s), 9.58 (1H, d, J=7.7Hz), 11.68 (1H, s), 14.26 (1H, broad)

Example 9

The following compounds were obtained according to a similar manner to that of Reference 1.

(1) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(4-imidazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

IR (Nujol): 3250, 1680, 1635, 1600, 1530 cm^{-1}

(2) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(4-imidazolylmethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR ($CDCl_3$, δ) : 4.85, 5.10 (2H, ABq, J=15Hz), 5.80 (1H, d, J=8Hz), 6.80-7.83 (15H, m), 8.10 (1H, d, J=8Hz), 10.10 (1H, broad s)

(3) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.04 (2H, ABq), 5.63 (1H, d, J=7.9Hz), 6.9-8.2 (15H, m), 9.58 (1H, d, J=7.9Hz), 11.65 (1H, s), 11.92 (1H, s)

(4) (3R)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.04 (2H, ABq), 5.62 (1H, d, J=7.9Hz), 6.9-8.3 (15H, m), 9.58 (1H, d, J=7.9Hz), 11.66 (1H, s), 11.93 (1H, s)

(5) (3RS)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-(2-imidazolylmethyl)-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 5.10 (2H, s), 5.65 (1H, d, J=8Hz), 6.60-8.10 (16H, m), 9.36 (1H, d, J=8Hz), 11.65 (1H, br s), 11.90 (1H, br s)

(6) (3Rs)-1,3-Dihydro-3-(2-indolylcarbonylamino)-1-[2-(4-imidazolyl)ethyl]-5-phenyl-2H-1,4-benzodiazepine-2-one

NMR (DMSO-d_6, δ) : 2.63 (2H, t, J=7Hz), 3.85-4.20 (1H, m), 4.20-4.75 (1H, m), 5.55 (1H, d, J=8Hz), 6.60 (1H, s), 6.93-7.85 (15H, m), 9.43 (1H, d, J=8Hz), 11.65 (1H, br s)

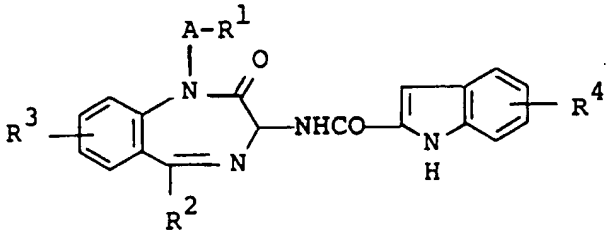
(7) (3S)-1,3-Dihydro-1-(4-imidazolylmethyl)-3-(2-indolylcarbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one hydrochloride

NMR (DMSO-d_6, δ) : 5.33 (2H, ABq), 5.69 (1H, d, J=7.6Hz), 7.0-8.0 (15H, m), 9.05 (1H, s), 9.60 (1H, d, J=7.6Hz), 11.74 (1H, s), 14.73 (1H, broad s)

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR,GB, IT, LI, LU, NL, SE

1. A compound of the formula :



wherein

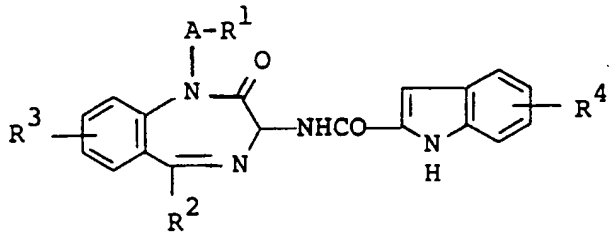
R^1 is tetrazolyl or imidazolyl,
R^2 is phenyl which may have a halogen,

R^3 is hydrogen or halogen,
R^4 is hydrogen, halogen or C_1-C_6 alkoxy and
A is C_1-C_6 alkylene,

and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, which is 1,3-dihydro-3-(2-indolylcarbonylamino)-5-phenyl-1-(5-tetrazolylmethyl)-2H-1,4-benzodiazepine-2-one

3. A process for preparing a compound of the formula :

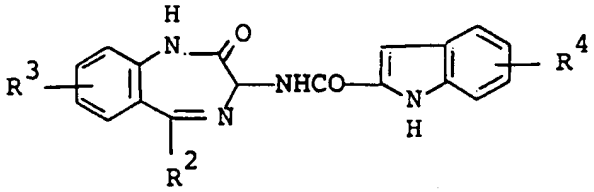


wherein

R^1 is tetrazolyl or imidazolyl,
R^2 is phenyl which may have a halogen,
R^3 is hydrogen or halogen,
R^4 is hydrogen, halogen or C_1-C_6 alkoxy and
A is C_1-C_6 alkylene,

or a salt thereof,
which comprises

(1) reacting a compound of the formula :

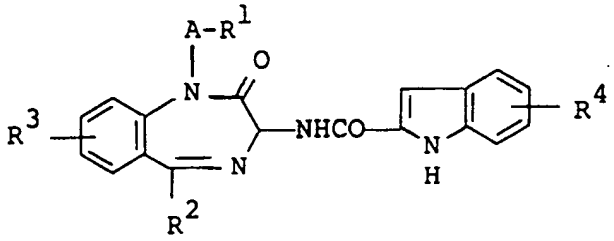


wherein R^2, R^3 and R^4 are each as defined above, or a salt thereof with a compound of the formula :

wherein

R^1 and A are each as defined above, and
X is halogen,

or a salt thereof to give a compound of the formula :

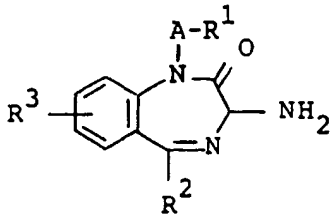


wherein

R^1, R^2, R^3, R^4 and A are each as defined above,

or a salt thereof, or

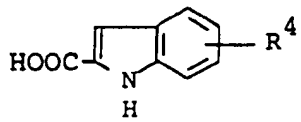
(2) reacting a compound of the formula :



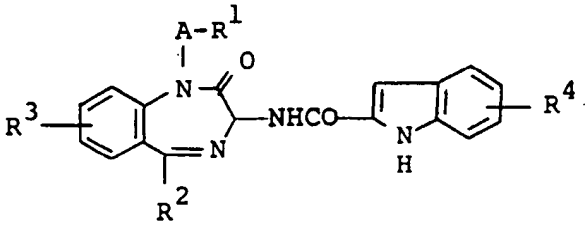
wherein

R^1, R^2, R^3 and A are each as defined above,

or its reactive derivative at the amino group or a salt thereof with a compound of the formula :



wherein R^4 is as defined above,
or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula :



wherein

R^1, R^2, R^3, R^4 and A are each as defined above,

or a salt thereof.

4. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

5. A compound of claim 1 or pharmaceutical acceptable salt thereof for use as a medicament.

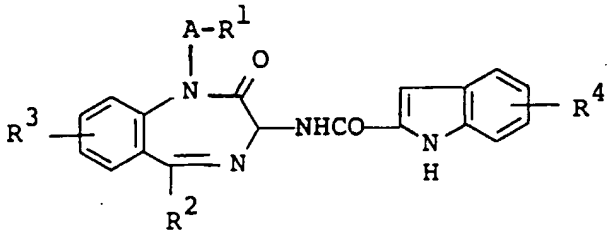
6. A compound of claim 1 or pharmaceutical acceptable salt thereof for use as a cholecystokinin antagonist.

7. A compound of claim 1 or pharmaceutical acceptable salt thereof for use in treating or preventing emesis or pancreatitis.

8. Use of a compound of claim 1 or pharmaceutical acceptable, salt thereof for the manufacture of a medicament for therapeutic treatment of emesis or pancreatitis.

Claims for the following Contracting States : ES, GR

1. A process for preparing a compound of the formula :

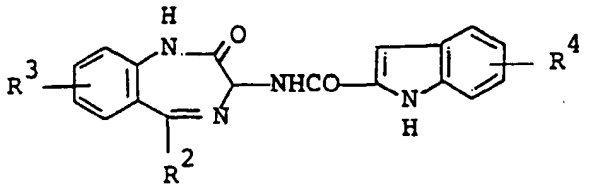


wherein

R^1 is tetrazolyl or imidazolyl
R^2 is phenyl which may have a halogen,
R^3 is hydrogen or halogen,
R^4 is hydrogen, halogen or C_1-C_6 alkoxy and
A is C_1-C_6 alkylene,

or a salt thereof,
which comprises

(1) reacting a compound of the formula :



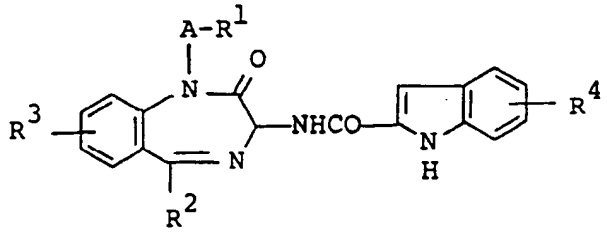
wherein R^2, R^3 and R^4 are each as defined above, or a salt thereof with a compound of the formula :

X-A-R^1

wherein

R^1 and A are each as defined above, and
X is halogen,

or a salt thereof to give a compound of the formula :

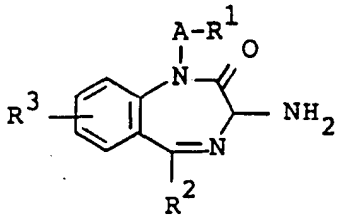


wherein

R^1, R^2, R^3, R^4 and A are each as defined above,

or a salt thereof, or

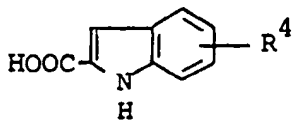
(2) reacting a compound of the formula :



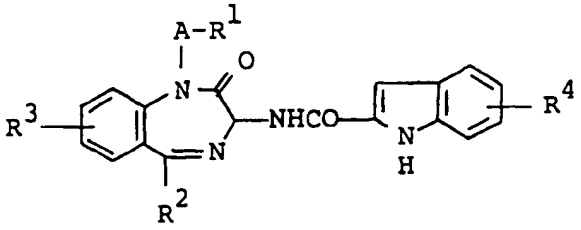
wherein

R^1, R^2, R^3 and A are each as defined above,

or its reactive derivative at the amino group or a salt thereof with a compound of the formula :



wherein R^4 is as defined above,
or its reactive derivative at the carboxy group or a salt thereof to give a compound of the formula :



wherein

R^1, R^2, R^3, R^4 and A are each as defined above,

or a salt thereof, and optionally converting the compound thereby obtained into the desired salt or optionally converting the salt thereby obtained into the desired free compound.

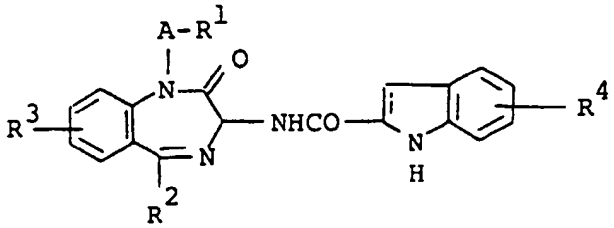
2. Process for preparing a pharmaceutical composition characterized by mixing a compound obtained by the process of claim 1 or a pharmaceutically acceptable salt thereof with at least one pharmaceutically acceptable substantially non-toxic carrier.

3. Modification of the process claimed in claim 1 which is characterized by bringing a compound of formula I or a non-toxic salt thereof, produced by a process claimed in claim 1, into pharmaceutically acceptable form by admixture or presentation of said compound with a pharmaceutically acceptable diluent or carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel:



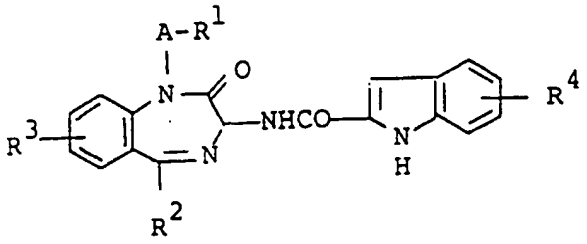
worin

R^1 Tetrazolyl oder Imidazolyl ist,
R^2 Phenyl ist, das Halogen aufweisen kann,
R^3 Wasserstoff oder Halogen ist,
R^4 Wasserstoff, Halogen oder (C_1-C_6)Alkoxy ist, und
A (C_1-C_6)Alkylen ist.

und ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, die 1,3-Dihydro-3-(2-indolylcarbonylamino)-5-phenyl-1-(5-tetrazolylmethyl)-2H-1,4-benzodiazepin-2-on ist.

3. Verfahren zur Herstellung einer Verbindung der Formel:

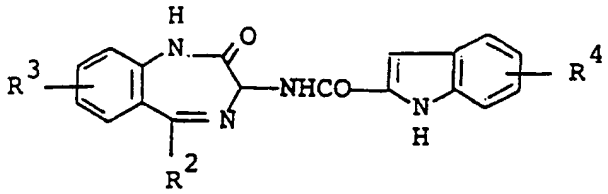


worin

R^1 Tetrazolyl oder Imidazolyl ist,
R^2 Phenyl ist, das Halogen aufweisen kann,
R^3 Wasserstoff oder Halogen ist,
R^4 Wasserstoff, Halogen oder (C_1-C_6)Alkoxy ist, und
A (C_1-C_6)Alkylen ist,

oder eines Salzes davon, das umfaßt:

(1) Reagieren einer Verbindung der Formel:



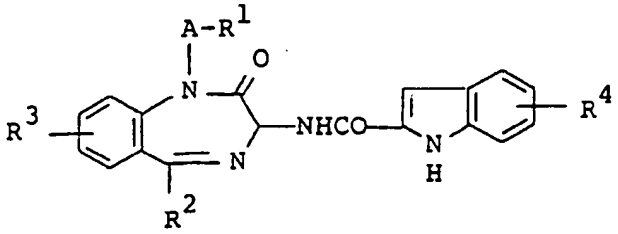
worin R^2, R^3 und R^4 jeweils wie oben definiert sind, oder eines Salzes davon mit einer Verbindung der Formel:

$$X\text{-}A\text{-}R^1$$

worin

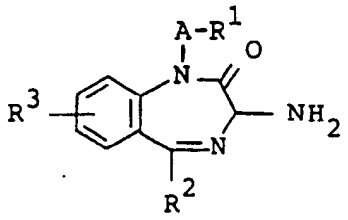
R^1 und A jeweils wie oben definiert sind und
X Halogen ist,

oder einem Salz davon, um eine Verbindung der Formel

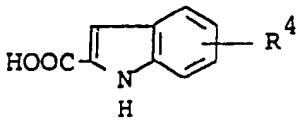


oder ein Salz davon zu ergeben, worin R^1, R^2, R^3, R^4 und A wie oben definiert sind, oder

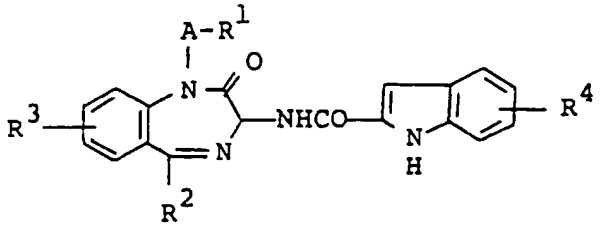
(2) Reagieren einer Verbindung der Formel:



worin R^1, R^2, R^3 und A wie oben definiert sind, oder eines reaktiven Derivates an der Aminogruppe oder eines Salzes davon mit einer Verbindung der Formel:



worin R^4 wie oben definiert ist,
oder ihrem reaktiven Derivat an der Carboxygruppe oder einem Salz davon, um eine Verbindung der Formel:



oder ein Salz davon zu ergeben, worin R^1, R^2, R^3, R^4 und A wie oben definiert sind.

4. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil eine Verbindung nach Anspruch 1 oder ein pharmazeutisches Salz davon in Zusammenmischung mit pharmazeutisch verträglichen Trägern umfaßt.

5. Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon zur Verwendung als Medikament.

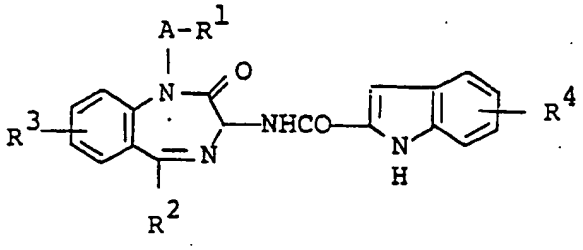
6. Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon zur Verwendung als Cholezystokinin-Antagonist.

7. Verbindung nach Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon zur Behandlung oder Prävention von Emesis oder Pancreatitis.

8. Verwendung der Verbindung nach Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon zur Herstellung eines Medikamentes zur therapeutischen Behandlung von Emesis oder Pancreatitis.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel:

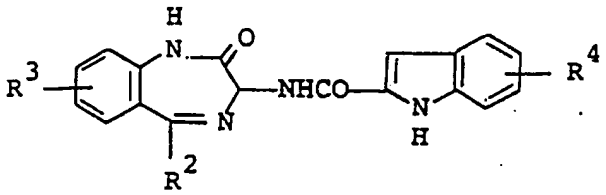


worin

R^1 Tetrazolyl oder Imidazolyl ist,
R^2 Phenyl ist, das Halogen aufweisen kann,
R^3 Wasserstoff oder Halogen ist,
R^4 Wasserstoff, Halogen oder (C_1-C_6)Alkoxy ist, und
A (C_1-C_6)Alkylen ist,

oder eines Salzes davon, das umfaßt:

(1) Reagieren einer Verbindung der Formel:



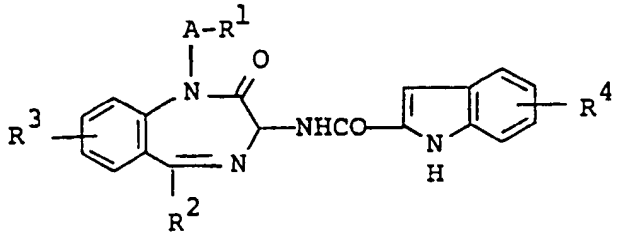
worin R^2, R^3 und R^4 jeweils wie oben definiert sind, oder eines Salzes davon mit einer Verbindung der Formel:

$$X\text{-}A\text{-}R^1$$

worin

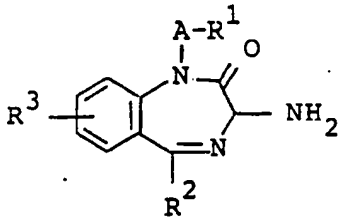
R^1 und A jeweils wie oben definiert sind und
X Halogen ist,

oder einem Salz davon, um eine Verbindung der Formel

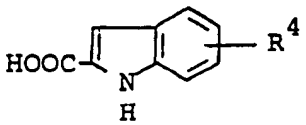


oder ein Salz davon zu ergeben, worin R^1, R^2, R^3, R^4 und A wie oben definiert sind, oder

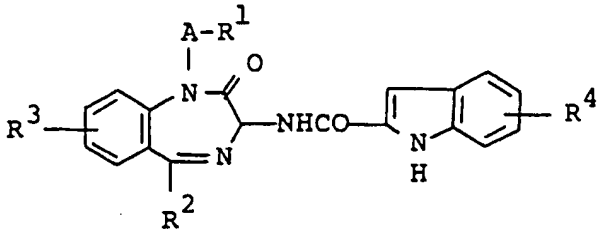
(2) Reagieren einer Verbindung der Formel:



worin R^1, R^2, R^3 und A wie oben definiert sind, oder eines reaktiven Derivates an der Aminogruppe oder eines Salzes davon mit einer Verbindung der Formel:



worin R^4 wie oben definiert ist,
oder ihrem reaktiven Derivat an der Carboxygruppe oder einem Salz davon, um eine Verbindung der Formel:



oder ein Salz davon zu ergeben, worin R^1, R^2, R^3, R^4 und A wie oben definiert sind, und wahlweise Überführen der so erhaltenen Verbindung in das gewünschte Salz oder wahlweise Überführen des so erhaltenen Salzes in die gewünschte freie Verbindung.

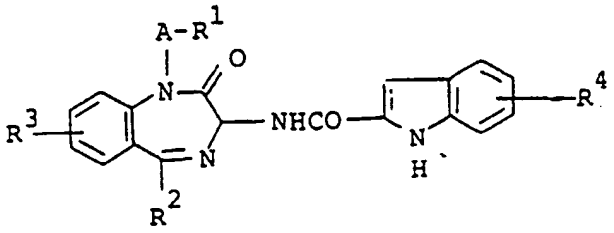
2. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, das gekennzeichnet ist durch Vermischen einer durch das Verfahren nach Anspruch 1 erhaltenen Verbindung oder eines pharmazeutisch verträglichen Salzes davon mit mindestens einem pharmazeutisch verträglichen, im wesentlichen nichtgiftigen Träger.

3. Modifizieren des Verfahrens nach Anspruch 1, das gekennzeichnet ist durch Überführen einer Verbindung der Formel I oder eines nicht-giftigen Salzes davon, die durch das in Anspruch 1 beanspruchte Verfahren hergestellt wurden in eine pharmazeutisch verträgliche Form durch Vermischen oder Präsentieren der genannten Verbindung mit einem pharmazeutisch verträglichen Verdünnungsmittel oder Träger.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de la formule :



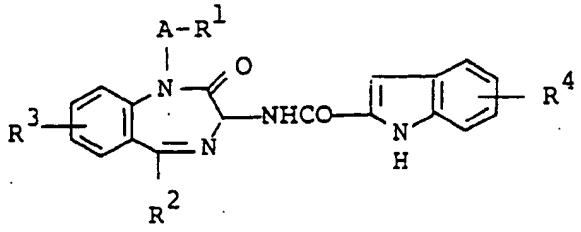
dans laquelle

R^1 est un groupe tétrazolyle ou imadazolyle,
R^2 est un groupe phényle qui peut avoir un atome d'halogène,
R^3 est un atome d'hydrogène ou d'halogène,
R^4 est un atome d'hydrogène, un atome d'halogène ou un groupe alcoxy en C_1-C_6 et
A est un groupe alkylène en C_1-C_6,

et un de ses sels pharmaceutiquement acceptables.

2. Composé de la revendication 1, qui est la 1,3-dihydro-3-(2-indolylcarbonylamino)-5-phényl-1-(5-tétrazolylméthyl)-2H-1,4-benzodiazépine-2-one.

3. Procédé pour préparer un composé de la formule :

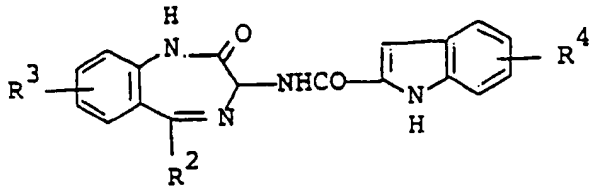


dans laquelle

R^1 est un groupe tétrazolyle ou imadazolyle,
R^2 est un groupe phényle qui peut avoir un atome d'halogène,
R^3 est un atome d'hydrogène ou d'halogène,
R^4 est un atome d'hydrogène, d'halogène ou un groupe alcoxy en C_1-C_6 et
A est un groupe alkylène en C_1-C_6,

ou un de ses sels,
qui comprend :

(1) La mise à réagir d'un composé de la formule :



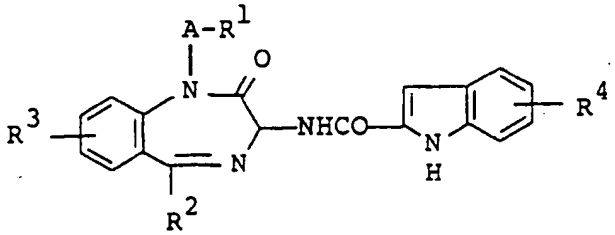
dans laquelle R^2, R^3 et R^4 sont chacun tels que définis ci-dessus, ou d'un de ses sels avec un composé de la formule :

$$X\text{-}A\text{-}R^1$$

dans laquelle

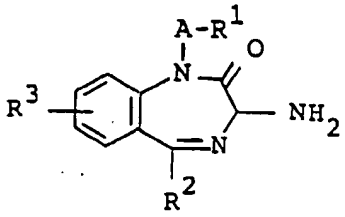
R^1 et A sont chacun tels que définis ci-dessus, et
X est un atome d'halogène,

ou un de ses sels pour donner un composé de la formule :

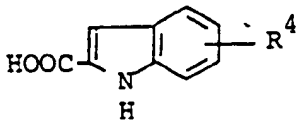


dans laquelle R^1, R^2, R^3, R^4 et A sont chacun tels que définis ci-dessus,
ou un de ses sels, ou

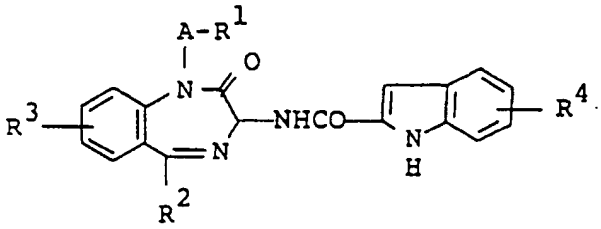
(2) La mise à réagir d'un composé de la formule :



dans laquelle R^1, R^2, R^3 et A sont chacun tels que définis ci-dessus,
ou son dérivé réactif au groupe amino
ou d'un de ses sels avec un composé de la formule :



dans laquelle R^4 est tel que défini ci-dessus,
ou son dérivé réactif au groupe carboxy,
ou un de ses sels pour-donner un composé de la formule :



dans laquelle R^1, R^2, R^3, R^4 et A sont chacun tels que définis ci-dessus,
ou un de ses sels.

4. Composition pharmaceutique qui comprend, comme ingrédient actif, un composé de la revendication 1 ou un de ses sels pharmaceutiquement acceptables en mélange avec des supports pharmaceutiquement acceptables.

5. Composé de la revendication 1 ou un de ses sels pharmaceutiquement acceptable pour emploi comme médicament.

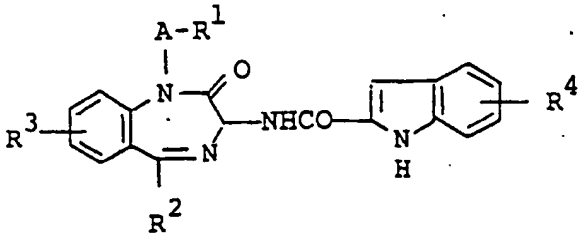
6. Composé de la revendication 1 ou un de ses sels pharmaceutiquement acceptables pour emploi comme antagonisme de la cholécystokinine.

7. Composé de la revendication 1 ou un de ses sels pharmaceutiquement acceptables pour emploi dans le traitement ou la prévention de l'émésise ou de la pancréatite.

8. Utilisation d'un composé de la revendication 1 ou d'un de ses sels pharmaceutiquement acceptables pour la fabrication d'un médicament pour le traitement thérapeutique de l'émésise ou de la pancréatite.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'un composé de la formule :

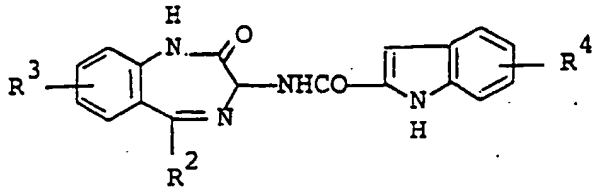


dans laquelle

R^1 est un groupe tétrazolyle ou imidazolyle,
R^2 est un groupe phényle qui peut avoir un atome d'halogène,
R^3 est un atome d'hydrogène ou d'halogène,
R^4 est un atome d'hydrogène, d'halogène ou un groupe alcoxy en C_1-C_6 et
A est un groupe alkylène en C_1-C_6,

ou d'un de ses sels,
qui comprend :

(1) La mise à réagir d'un composé de la formule :



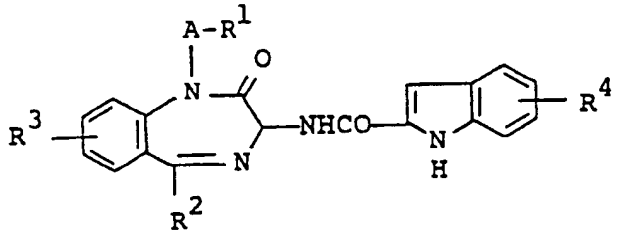
dans laquelle R^2, R^3 et R^4 sont chacun tels que définis ci-dessus,
ou d'un de ses sels avec un composé de la formule :

$$X\text{-}A\text{-}R^1$$

dans laquelle

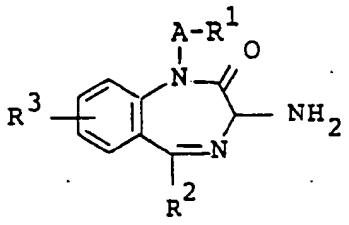
R^1 et A sont chacun tels que définis ci-dessus, et
X est un atome d'halogène,

ou un de ses sels pour donner un composé de la formule :

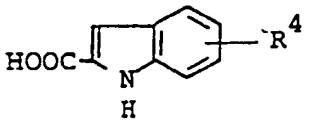


dans laquelle R^1, R^2, R^3, R^4 et A sont chacun tels que définis ci-dessus,
ou un de ses sels, ou

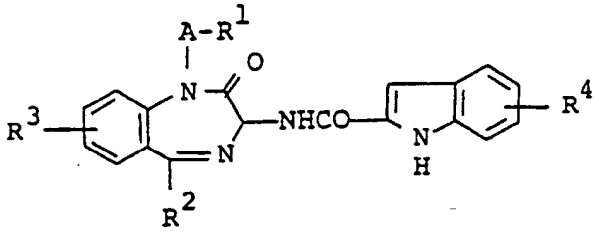
(2) La mise à réagir d'un composé de la formule :



dans laquelle R^1, R^2, R^3 et A sont chacun tels que définis ci-dessus,
ou de son dérivé réactif au groupe amino
ou d'un de ses sels avec un composé de la formule :



dans laquelle R^4 est tel que défini ci-dessus,
ou son dérivé réactif au groupe carboxy,
ou un de ses sels pour donner un composé de la formule :



dans laquelle R^1, R^2, R^3, R^4 et A sont chacun tels que définis ci-dessus,
ou un de ses sels, et en option la conversion du composé ainsi obtenu dans le sel désiré
ou en option la conversion du sel ainsi obtenu en le composé libre désiré.

2. Procédé pour préparer une composition pharmaceutique caractérisé par le mélange d'un composé obtenu par le procédé de la revendication 1 ou un de ses sels pharmaceutiquement acceptables avec au moins un support pharmaceutiquement acceptable, sensiblement non toxique.

3. Modification du procédé revendiqué en revendication 1 qui est caractérisée en ce qu'on amène un composé de la formule I ou un de ses sels non toxiques, obtenu par le procédé revendiqué en revendication 1, sous une forme pharmaceutiquement acceptable par mélange ou présentation dudit composé avec un diluant ou un support pharmaceutiquement acceptables.